Objection Under 37 C.F.R. 1.75(c)

The Office has objected to claim 14 as "being of improper dependent form for failing to further limit the subject matter of a previous claim." Office Action at page 9. Applicants respectfully traverse. However, merely to expedite prosecution, Applicants have canceled claim 14. Accordingly, Applicants respectfully request the withdrawal of the objection.

Rejection Under 35 U.S.C. § 112, second paragraph

Applicants acknowledge the Office's withdrawal of the rejection, based on 35 U.S.C. § 112, second paragraph, of claim 12.

The Office has maintained its rejection of claim 2 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action at page 3.

Applicants respectfully traverse. However, merely to expedite prosecution, Applicants have amended claim 2 by deleting the term "coding" as the Office suggested. Accordingly, the rejection should be withdrawn.

Rejections Under 35 U.S.C. § 103

The Office has maintained the rejection of claims 1-3 and 5-14 under 35 U.S.C. § 103(a) as "being unpatentable over Hao et al. (Human Gene Therapy (July 1995) 6: 873-880) in view of Uzan et al. (J. Biol. Chem. (1991) 266(14): 8932-8939)." Office

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Action at page 4. Further, the rejection of claim 4 under 35 U.S.C. § 103(a) was reinstated as being unpatentable over Hao et al. and Uzan et al. and further in view of Kurachi et al. (J. Biol. Chem. (1995) 279(10):5276-5281). Office Action at page 7.

As set forth in M.P.E.P. § 2143.01, in order to establish a *prima facie* case of obviousness the Office must meet three criteria. "First, there must be some suggestion or incentive, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (M.P.E.P. § 2143.01 and cases cited therein.)

As explained below, the Office has failed to establish a *prima facie* case of obviousness because the prior art cited by the Office does not give guidance or evidence that one of skill in the art would be motivated to combine the DNA construct disclosed in Hao with the promoter disclosed in Uzan. Further, a skilled artisan would not reasonably expect to succeed in expressing Factor IX in hematopoietic cells using a hematopoietic-specific promoter if he were to combine Hao and Uzan. The addition of Kurachi does not cure this defect. Accordingly, the rejections of claims 1-14 should be withdrawn.

The Office has stated that Applicant "appears to be attacking the references individually and one cannot show nonobviousness by attacking references individually

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where the rejections are based on a combination of references." Office Action at page 6. Applicant respectfully submits that in order to address an obviousness rejection, even one based on a combination of references, each reference must be discussed. Applicant has addressed each of the references and has explained why one of skill in the art would not be motivated to combine them or, if combined, would not have a reasonable expectation of success.

Applicant believes that there is no motivation to combine the DNA construct of Hao with the promoter of Uzan because Hao does not require targeted expression and, in fact, teaches away from such targeting. Specifically, Hao's stated goal is to develop an "autologous bone marrow transplantation with factor IX-transduced cells for the treatment of hemophilia B." (Hao; page 874, left column, second full paragraph.) Because Hao teaches isolation and removal of the specific cells of interest from the body, transduction of the construct *ex-vivo*, and then reimplantation, Hao's DNA construct does not require targeting, let alone targeting via the GPIIb promoter disclosed in Uzan.

Further, Hao teaches "factor IX gene transduction of all the stem cells in a marrow inoculum" and adds that "[t]his tremendous mass of cells could, theoretically, become a rich source of endogenously produced coagulant or other needed circulating protein." (Hao; page 878, right column, second full paragraph.) Thus, Hao teaches

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away from targeting Factor IX to a specific cell-type such as megakaryocytes because such targeting may result in insufficient production of Factor IX.

Hao does mention the use of hematopoietic-specific promoters to target expression. (Hao; page 879, left column, second full paragraph.) Hao's statement, however, is nothing more than pure speculation as it is preceded by the suggestion that ideally, all hematopoietic cells should be transduced. For these reasons, one of skill in the art would not be motivated to add the GPIIb promoter disclosed in Uzan to the DNA construct disclosed in Hao, as such a combination is unnecessary based on Hao's disclosure.

Not only do the references fail to motivate one of skill in the art to combine the DNA construct of Hao with the promoter disclosed in Uzan, the references also fail to provide a reasonable expectation of success. Hao merely speculates as to the possibility of targeting Factor IX expression to a specific lineage. (Hao; page 879, left column, second paragraph.) However, there is no guidance as to what specific hematopoietic cell types should be targeted or whether any specific hematopoietic cell type would successfully express Factor IX. In fact, Hao states "[i]t is not known which specific hematopoietic cell type(s) would be best for expression of factor IX." *Id.*

Similarly, Uzan identifies a promoter region of the GPIIb gene that is necessary to direct the expression of GPIIb itself in megakaryocytic cells, but then merely suggests that this region "could be used to target the expression of heterologous genes in vivo."

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(Uzan; page 8938, right column, last sentence (emphasis added).) Thus, without experimentation, one of skill in the art would not know whether this promoter region can be used to direct the expression of any heterologous gene, let alone Factor IX.

Taking Hao and Uzan together, there is no reasonable expectation of successfully targeting expression of Factor IX to megakaryocytes, as Uzan does not know whether the GPIIb promoter could be used to target expression of heterologous genes other than GPIIb itself. And if targeting is successful, there is no reasonable certainty that the targeted cell could successfully express Hao's DNA construct. Simply stated, even if a specific hematopoietic cell such as megakaryocytes were found to have the machinery capable of expressing Factor IX, it is still not obvious that the promoter region identified by Uzan could be used to direct Factor IX expression to megakaryocytes.

The Office has stated that Applicant has not provided any evidence that one of skill in the art would not have a reasonable expectation of success. Office Action at page 7. It is the Office, however, that has not established that there is a reasonable expectation of success given the abundance of evidence to the contrary in Hao and Uzan identified herein and in previous responses by the Applicant.

The Office has failed to establish a *prima facie* case of obviousness for at least the reasons stated above. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 1-14.

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If there is any fee due in connection with the filing of this Statement, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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